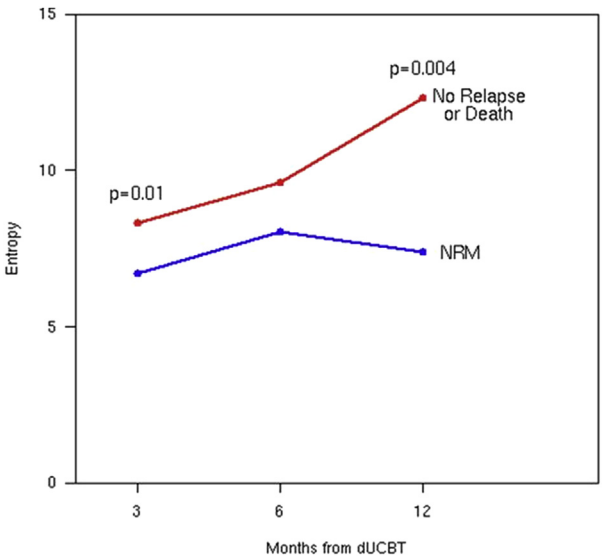
function is crucial to identify those at risk and institute pre-emptive therapies. We hypothesize that T-cell receptor (TCR) diversity after double umbilical cord blood transplantation (dUCBT) will predict clinical outcomes.

Methods: 42 adult dUCBT recipients received fludarabine, melphalan, ATG with tacrolimus/sirolimus as GvHD prophylaxis. TCRb CDR3 regions were amplified from unsorted PBMCs and sequenced using the ImmunoSeq platform (Adaptive Biotechnologies) at 3, 6 and 12 months after dUCBT. Samples analyzed had predominantly donor T-cell chimerism and no morphologic relapse. We analyzed 34 samples at 3 mos, 26 at 6 mos and 23 at 12 mos. Entropy/Shannon's diversity index and richness/Fisher's alpha diversity were calculated from number and frequency of TCRb sequences and normalized for sequencing depth. Higher entropy and richness, measures of uncertainty and unseen species within a complex population, reflect increased diversity.

Results: Median age was 52 years (19-67). 57.1% were in remission at dUCBT. Primary indications for dUCBT were AML, NHL and MDS. Median follow-up among survivors was 47 months (18-91). 4-year OS was 41%; 4-year PFS was 26%. As a whole, dUCBT recipients increased entropy and richness of their T cell repertoire in the first year. We categorized subjects into 3 groups: relapse, NRM, or alive with neither event. In the NRM cohort, median entropy and richness values rose slightly from 3 to 6 mos then fell at 12 mos. In comparison, median entropy and richness were higher in the no event cohort between 3 and 12 mos and rose substantially to diversity levels found in healthy donors. ($p=0.01$, 0.09, 0.004 for entropy at 3,6,12 mos; $p=0.06$, 0.11, 0.006 for richness at 3,6,12 mos). (Figure) Entropies of subjects who relapsed did not differ from those of the no event cohort (not depicted). In a similar analysis, entropy values for subjects with chronic GvHD fell between 3 and 12 mos and were significantly lower than in subjects without any cGvHD, relapse, or NRM at 12 mos (median entropy 5.9 vs 12.3, $p=0.04$). In multivariable analyses controlling for age, patient sex, disease status, and diagnosis, high entropy was associated with lower NRM (HR 0.68, $p<0.001$), PFS (HR 0.79, $p=0.009$) and OS (HR 0.73, $p=0.005$). High richness (log10 transformed) was associated with lower NRM (HR 0.3, $p<0.001$) and OS (HR 0.30, $p=0.0003$).

Conclusion: T-cell repertoire diversity as early as 3 months after dUCBT is significantly lower in subjects who eventually experience NRM or cGvHD and does not expand with time after transplant. These quantitative predictive indices may be used to identify dUCBT recipients who merit more intensive monitoring or prophylactic strategies against infection and GvHD.



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Cytomegalovirus-Tissue Invasive Disease in Allogeneic Hematopoietic Cell Transplant in the Setting of a Preemptive Strategy

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Background: Monitoring of cytomegalovirus (CMV) DNA by PCR followed by preemptive treatment of CMV viremia (CMVV) is an acceptable preventive strategy to reduce the incidence of CMV tissue invasive disease (TID) after allogeneic hematopoietic cell transplant (HCT). Despite proactive monitoring, some patients develop CMV TID leading to adverse outcomes. We seek to characterize risk factors associated with the development of CMV TID in HCT recipients who were monitored and treated preemptively.

Methods: We reviewed the charts of 256 adult HCT recipients, actively monitored for CMVV between January 1, 2009 and July 31, 2013. Our center preemptively monitors allogeneic HCT recipients with weekly CMV DNA by PCR until Day + 100, and thereafter every 2 weeks in patients with GVHD. Antiviral therapy was initiated within 1 day of identifying significant CMVV. Patients with CMV TID occurring during preemptive monitoring were matched 1:1 by the underlying disease, year of transplant, and time of follow-up with controls that developed CMVV without TID.

Results: Of the 15 patients that developed CMV TID despite preemptive therapy, 10 (66.7%) occurred within the first 100 days following HCT. Median time from HCT to CMV TID was 62 days (range 25 -1137). All cases were gastrointestinal CMV TID with 1 case of CMV-associated oral mucositis. 9/15 (60%) had concurrent CMVV at the time of CMV TID diagnosis, and 4/15 (26%) were preemptively being treated with antivirals for CMVV at the time of CMV TID diagnosis. The mean viral load was 1,738.5 copies DNA/mL, range (0-9,699 copies DNA/mL). 6/15 (40%) had at least one prior episode of CMVV which had previously resolved. When compared with controls there were no significant differences in age, type of HCT, time to CMV TID, conditioning therapy, donor matching, comorbidities, GVHD, level of initial CMVV, or CMV donor/recipient serological status. No ganciclovir resistance was identified in patients with CMV TID.

Conclusions: All cases of CMV TID were gastrointestinal disease and tended to occur early after HCT. CMV TID developed in the majority without preceding viremia. There were no risk factors that could specifically identify patients likely to develop CMV TID despite pre-emptive monitoring and treatment. Gastrointestinal CMV TID remains an inherent complication of a CMV preemptive strategy.

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Co-Stimulatory Blockade Permits Transplantation of Human Hematopoitic Stem Cells and HLA Incompatible T Cells in NOD/SCID γ Null (NSG) Mice

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